14. (Amended) A method of preventing or treating HPV induced tumors in a patient comprising administering a safe and effective amount of a composition as claimed in claim 1.

15. (Thrice Amended) A method of preparing a composition as claimed in any one of claims 1, or 3-11 comprising admixing an isolated fusion protein selected from the group consisting of: E6 protein, E7 protein, and E6/E7 fusion protein, linked to a protein D or a fragment thereof having T helper epitopes from ~~*Heamophilus influenzae*~~ *Haemophilus influenza* B, lipoprotein D or fragment thereof having T helper epitopes from ~~*Heamophilus influenzae*~~ *Haemophilus influenza* B, and an immunostimulatory CpG oligonucleotide.

REMARKS

Claims 1-11 and 13-20 are pending in the application. No claims have been allowed. Claims 1-11 and 13-20 are rejected. No claims stand objected to. Applicants cancelled claims 2, 12 and 16-20 without prejudice and amended claims 1, 6, 8, 10, 11 and 13-15. Claims 1, 6, 8, 10, 11 and 13-15 have been amended for the following reasons:

Claim 1 - to indicate that the isolated fusion proteins are selected from the group consisting of E6 or E7 protein and E6/E7 fusion protein from HPV, to delete the term "optionally", to further define the immunological fusion partner as protein D or a fragment thereof having T helper epitopes from *Heamophilus influenzae* B, lipoprotein D or fragment thereof having T helper epitopes from *Heamophilus influenzae* B, and to a further define CpG as cytosine-guanosine;

Claim 6- to change dependency to claim 1 and

Claim 10 - to change dependency to claim 1;

Claim 13 - to change dependency to claim 1;

Claim 14 - to change dependency to claim 1;

Claim 15 - to change dependency to claims 1 or 3-11, and to indicate that the isolated fusion proteins are selected from the group consisting of E6 or E7 protein and E6/E7 fusion protein from HPV, to delete the term optionally and to further define the immunological fusion partner as protein D or a fragment thereof having T helper epitopes

from Heamophilius influenzae B, lipoprotein D or fragment thereof having T helper epitopes from Heamophilius influenzae B.

The Declaration of Dr. Catherine Gérard ("Gérard Dec.") is submitted herewith in support of Applicants' position of patentability.

In view of the following amendment and response, the Applicants believe the claims presented herein are allowable. Reconsideration is respectfully requested. Applicants remarks below will be made in the context of the claim set remaining after this amendment.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Rejections under 35 USC §112, second paragraph

The Examiner has rejected claims 1-2 and 15 as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

Initially, Applicants respectfully submit that the cited art, including Edwards WO 96/19496, does not contemplate compositions comprising E6, E7 or E6E7 and a CpG oligonucleotide. Contrary to the Examiner's statement, Edwards does not disclose a composition comprising HPV E6, E7, E6E7, whether unmodified or in fusion, with another fusion partner, in combination with a CpG oligonucleotide, as claimed by the present invention. Although there is a general reference made to the addition of an adjuvant in Edwards' pharmaceutical composition comprising the E6, E7 variant proteins (page 10, first paragraph), there is no disclosure of any specific adjuvant, nor of any preferred adjuvant, let alone of CpG.

Nevertheless, in the interest of securing a patent expeditiously, Applicants have amended claims 1 and 15 to delete the term "optionally" to address the rejection and to limit the claim to indicate that the fusion partner is not any fusion partner. Claim 2 has been cancelled. Applicants reserve the right to pursue the broader claims in a divisional application.

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Rejections under 35 U.S.C. § 103

Claims 1-11 and 13-16 have been rejected under 35 U.S.C. § 103 as obvious over a number of references. Applicants have cancelled claims 2 and 16 and amended claims 1, 10 and 13-15. Applicants reserve the right to pursue the broader and the cancelled claims in a divisional application. The rejection of the uncancelled claims is addressed below.

Edwards

As noted above, Applicants respectfully submit that Edwards does not disclose a composition comprising HPV E6, E7, E6E7, whether unmodified or in fusion, with another fusion partner, in combination with a CpG oligonucleotide as claimed by the present invention. Nevertheless, Applicants have amended the claims (claims 1 and 15 specifically) to indicate that E6, E7 or E6/E7 are linked to protein D or a fragment thereof having T helper epitopes from Heamophilius influenzae B, lipoprotein D or fragment thereof having T helper epitopes from Heamophilius influenzae B and are combined with an immunostimulatory CpG oligonucleotide containing an unmethylated CpG dinucleotide to secure the allowance of the patent.

Boursnell, et al.

The Examiner maintains that it would have been obvious to combine the modified E6 and E7 antigens with oligonucleotides containing CpG motifs, especially since Chu, *et al.* disclose that the CPG oligonucleotides redirect a TH2 response to a CTL TH1 response. Applicants traverse this rejection and respectfully submit that the claims, as now amended, are not obvious over Boursnell, *et al.*, alone or in combination with Chu, *et al.* Boursnell, *et al.* disclose the construction and characterization of a recombinant **vaccinia** virus designed to express modified forms of E6 and E7 from HPV16 and HPV18 (see the abstract). Further, Boursnell, *et al.* indicate that their modified forms of E6 and E7 from HPV16 and HPV18 induce an HPV-specific CTL response against HPV-induced cervical cancer. Boursnell, *et al.* further report the construction and characterization of a recombinant vaccinia virus expressing the E6 and E7 proteins from HPV types 16 and 18. The recombinant virus was shown to be less neurovirulent compared to the parental strain and capable of inducing an HPV-specific CTL response. However, the disclosure by Boursnell, *et al.* does not enable one skilled in the art to

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broadly apply the teachings to future developments envisioned in the field of HPV-induced tumors therapy. Despite the fact that this recombinant vaccinia virus is shown to induce CTL at least against E7 of HPV16, it was not demonstrated for HPV18-derived proteins. Moreover, neither the best way to induce CTL against these antigens, nor their clinical significance was disclosed in Boursnell, *et al.* (Gérard Dec. ¶ 4 and 5).

In contrast to Boursnell, *et al.*, who describe the induction of CTL against E6 and E7 proteins using a recombinant vaccinia virus/vector-type approach without identifying a clinical significance to the finding, the present inventors have discovered a composition comprising a CpG oligonucleotide and proteins D E7, D E6 or D E6E7, will be effective in the generation of a CTL response and that such immunological response will lead to tumor regression in a tumor model. (Gérard Dec. ¶ 5).

The present invention as claimed in the amended claims is directed to a E6, E7 or E6/E7 fusion protein from HPV linked to protein D or fragment thereof having retained T helper epitopes, and an immunostimulatory CpG oligonucleotide containing an unmethylated CpG dinucleotide. This composition is neither disclosed nor suggested by the art of record. Furthermore, not only does the present invention demonstrate the effectiveness of CTL in tumor regression in an E7 expressing tumor model, it also shows the induction of a broader immune response, including CD4 proliferation and an E7-specific antibody response. (Gérard Dec. ¶ 6). Furthermore, in contrast to the vaccinia-based approach disclosed in Boursnell, *et al.*, these results have been generated with a protein-based approach in th present application. (Gérard Dec. ¶ 6).

One skilled in the art would not have been motivated to change the method of delivery of early antigens from a viral vector approach to a protein/adjuvant approach. Nor is there suggestion to combine the various elements as they appear in the amended claims. The data obtained with a live vector approach cannot be extrapolated to the subunit protein/adjuvant approach of the present invention.

Furthermore, the CTL response is only an aspect of the immune response against a given antigen. The composition claimed in amended claim 1 has been demonstrated to mount, not only a CTL response, but also an antibody response against the antigen – a result that one skilled in the art could not have possibly predicted or anticipated by reading Boursnell, *et al.*

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Finally, applicants submit that the composition of the present invention provides excellent efficacy especially in the regression of tumor load in two different animal models. Such data shows the strong therapeutic potential of the claimed composition. (Please see Examples XIII and XV in the specification).

Chu, et al.

Chu, *et al.* teach that synthetic CpG oligodeoxynucleotides act as adjuvants that switch on T helper 1 (Th1) immunity thereby making them attractive adjuvant candidates for a wide range of infectious diseases and immune disorders (see page 1630, right column lines 1-3). Chu is not concerned with providing an effective composition against HPV-induced tumors, it addresses a different problem.

Edwards, Boursnell, et al. & Chu, et al. taken together

The Examiner takes the position that it was obvious to combine CpG, disclosed by Chu, *et al.* to be able to redirect a TH2 response to a CTL TH1 response, with the modified E6 and E7 antigens and that the result was not unexpected. The Applicants disagree and submit that the claims, as amended, are not obvious over the combined references. None of the cited references are directed to compositions comprising a CpG oligonucleotide and an HPV-derived antigen, nor do they suggest the need for improved HPV formulations especially formulations in the form of specific HPV antigens-CpG compositions. Applicants were the first to disclose such compositions and demonstrated that such compositions are effective in reducing or destroying HPV-induced tumors.

Edwards and Boursnell, *et al.* do not suggest the need for an improved antigenic formulation against HPV-induced cancers, nor do they suggest the use of a Th1 adjuvant in general and CpG in particular. It was not obvious at that time of the present invention that a vaccine made of a purified protein formulated in an aqueous solution with CpG ODN would lead to the generation of CTL and would lead to tumor rejection (Gérard Dec. ¶ 7).

Although the publication from Chu, *et al.* disclosed that CpG could work as an adjuvant that switches on TH1 immunity, at least when it was combined with Hen Egg Lyzozyme (HEL) antigen, it was not obvious at the time the Applicants were conducting their experiments that CpG ODN would work with **any** antigen, especially with **cancer** antigens (Gérard Dec. ¶ 8).

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Finally, the present invention demonstrates a synergistic effect, *i.e.*, the CpG/antigen composition is more effective than a composition comprising either component individually (see specification, Figures 1 and 2).

In view of the amendments and remarks above, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. § 103.

Rejections under 35 USC §112 first paragraph

The Examiner rejected claim 19 under 35 USC §112, first paragraph. Applicants have deleted claim 19 and, therefore, the rejection is now moot.

Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 1, 7, 17 and 18 and 20 under 35 U.S.C. §103(a) as being unpatentable over Gissman, *et al.* and further in view of Chu, *et al.* Claims 17, 18 and 20 have been deleted, therefore, the rejection of these claims is now moot.

With respect to claims 1 and 7, Applicants respectfully traverse the rejection. Gissman, *et al.* disclose vaccine formulations comprising viral **capsomeres**. More specifically, Gissman, *et al.* teach antigen formulations wherein the antigen is a fusion between L1 and another polypeptide other than L1 protein and processed as a capsomere. The secondary antigen, which may be an HPV early antigen, is designed to inhibit VLP particle formation (through deletions for example). As discussed above, Chu, *et al.* each that synthetic CpG oligodeoxynucleotides act as adjuvants that switch on T helper 1 (Th1) immunity from a Th2 immunity. Chu is not concerned with providing an effective composition against HPV-induced tumors.

As acknowledged by the Examiner, Gissman, *et al.* do not teach an immune composition containg an HPV antigen and a CpG oligonucleotide. Applicants further submit that Gissman, *et al.* also do not teach or suggest the present invention as claimed in the amended claims which covers a composition comprising an isolated fusion protein selected from the group consisting of E6 or E7 protein and E6/E7 fusion protein from HPV, linked to protein D or a fragment thereof having T helper epitopes from Heamophilius influenzae B, lipoprotein D or fragment thereof having T helper epitopes

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from Heamophilius influenzae B, and an immunostimulatory CpG oligonucleotide containing an unmethylated CpG dinucleotide.

It is well illustrated in the literature that HPV late and early antigens play different roles in HPV-induced infections and lesions (please see Ullman & Emery, a copy of which has been attached to Applicants response dated June 28, 2001). For example, in the table on page 40 in the article, L1 and L2 are described as two structural components of the viral virion capsid, and the early antigens, such as E6, E7 as functional proteins. Furthermore, L1 and L2 proteins are known to form VLPs or capsomeres (see Gissman, *et al.*), they are immunogenic by themselves and are capable to induce antibody responses able to protect against HPV infection (Gérard Dec. ¶ 9).

In contrast to the present invention, Gissman, *et al.* suggests positioning the second protein, whatever it might be, to **inhibit** the formation of VLP. The engineered capsomeres are the effective component of Gissman, *et al.*'s vaccine formulation (see column 7, lines 24-29) and were shown to elicit neutralising antibodies in immunised mice (see Example 7, column 16, lines 16-19). There is no reason for one skilled in the art reading Gissman, *et al.* to depart from the Gissman, *et al.* invention and i) chose as a core component an early antigen of HPV, in particular E6 and E7; ii) fuse this early antigen to protein D, a protein from *Haemophilus influenzae*; iii) add to this components a CpG oligonucleotide with the expectation that the combination would be a success. Furthermore, Chu, *et al.*, as discussed above, does not complete the teaching of Gissman, *et al.* In view of the amendments and remarks above, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. § 103(a).

In view of the above amendments and remarks, which Applicants believe are fully responsive to the outstanding Office Action, Applicants respectfully request reconsideration of the rejection of the claims and allowance of all claims in the application. The Examiner is invited to contact Applicants' undersigned attorney at the

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number provided below if this might facilitate the allowance of this case.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 2, 12 and 16-20 have been canceled.

Claims 1, 6, 8, 10, 11 and 13-15 have been amended as follows:

1. (Twice Amended) A composition comprising an isolated fusion protein, wherein said composition comprises a Human Papilloma Virus (HPV) protein selected from the group consisting of: E6 protein,[or] E7 protein, [or]and E6/E7 fusion protein[from HPV optionally], linked to [an immunological fusion partner having T helper epitopes]a protein D or a fragment thereof having T helper epitopes from *Heamophilius influenzae* B, lipoprotein D or fragment thereof having T helper epitopes from *Heamophilius influenzae* B, and an immunostimulatory cytosine-guanosine (CpG) containing oligonucleotide.[CpG oligonucleotide containing an unmethylated CpG dinucleotide.]

6. (Amended) A composition as claimed in claim 1[any of claims 1 to 5] additionally comprising a histidine[hisitidine] tag of at least 4 histidine[hisitidine] residues.

8. (Thrice Amended) A composition as claimed in claim 1 wherein the immunostimulatory CpG oligonucleotide comprises a hexamer motif: purine purine cytosine guanine[guaine] pyrimidine pyrimidine.

10. (Amended) A composition as claimed in claim 1[herein] wherein the CpG oligonucleotide contains a phosphorothioate inter-nucleotide linkage.

11. (Amended) A composition as claimed in claim 1[herein] wherein the CpG oligonucleotide is selected from the group consisting of:

OLIGO 1: TCC ATG ACG TTC CTG ACG TT;

OLIGO 2: TCT CCC AGC GTG CGC CAT; and

OLIGO 3: ACC GAT GAC GTC GCC GGT GAC GGC ACC ACG.

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13. (Amended) A method of inducing an immune response in a patient to an HPV antigen comprising administering a safe and effective amount of a composition as claimed [herein]in claim 1.

14. (Amended) A method of preventing or treating HPV induced [tumours]tumors in a patient comprising administering a safe and effective amount of a composition as claimed [herein]in claim 1.

15. (Thrice Amended) A method of preparing a composition as claimed in any one of claims[1-11 or 16,] 1, or 3-11 comprising admixing an isolated fusion protein selected from the group consisting of: E6 protein, E7 protein, [or] and E6/E7 fusion protein [optionally], linked to [an immunological fusion partner having T helper epitopes] a protein D or a fragment thereof having T helper epitopes from *Heamophilius influenzae* B, lipoprotein D or fragment thereof having T helper epitopes from *Heamophilius influenzae* B, and an immunostimulatory CpG oligonucleotide.

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